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EXAMINER	
ROBINSON, HOPE A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,369	VAN DEN BERG, MARCO ALEXANDER	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-25 and 27-38* is/are pending in the application.

4a) Of the above claim(s) *10-14,21 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 15-20 and 27-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed November 26, 2008 on March 26, 2009 is acknowledged, however, the Office Action has been vacated in favor of the following.

Claim Disposition

2. Claims 29-38 have been added. Claims 1-21, 23-25 and 27-38 are pending. Claims 1-9, 15-20 and 27-38 are under examination based on the rejoinder of claims in the Petition Decision mailed November 23, 2009. Claims 10-14, 21 and 23-25 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claim Objection

3. Claims 1-9, 17-20, 32-38 are objected to because of the following informalities:

For clarity and precision of claim language it is suggested that claim 1 is amended to read, "...compared to a non-transfected host cell; and wherein the label provides a non-inheritable trait to the host cell".

For clarity and precision of claim language it is suggested that claims 2-9, 17-20, 27-28, 30, 32-34 and 36-38 are amended to read "The method of claim …, wherein…". For clarity it is suggested that claim 7 is amended to read, "or another marker that is an inheritable trait" (see also claim 36).

Claims 32 to 38 are objected to because the numbering of the claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 32-38 have been renumbered 31-37.

For clarity it is suggested that claim 15(a) is amended to read, " provides a non-inheritable trait to the host cell". In addition, item (d) should be amended to recite, "host cells that have the DNA integrated in its ….lost in the transfected host cell progeny".

For clarity claim 35(c) should be amended to read, "culturing the host cells containing the fluorescent label..."

Correction is required.

Maintained and Amended-Claim Rejections - 35 USC э 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9, 15-20 and 27-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas,

etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers,* 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents" of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli,* the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for *a prima facie* case is discussed below.

Further, to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: a) the scope of the invention; b) actual reduction to practice; c) disclosure of drawings or structural chemical formulas; d) relevant identifying characteristics including complete structure, partial structure, physical and/or

chemical properties, and structure/function correlation; e) method of making the claimed compounds; f) level of skill and knowledge in the art; and g) predictability in the art.

The claimed invention is directed to a method for preparation of a modified host cell comprising transfecting a host cell with at least one polynucleotide to which a label is covalently coupled; and isolating the transfected host cell, wherein said at least one polynucleotide permanently changes a metabolic property of the transfected host cell as compared to the non-transfected host cell; wherein the label provides to the host cell a non-inheritable trait. The claimed invention lacks adequate written description with respect to the claimed method step resulting in a permanent change in a metabolic property of the host cells. The instant specification describes the pGBDEL4L plasmid that is transfected in the host cell (*Penicillium crysogenum*) and the use of fluorescein as a label and describe a metabolic change as being a change in metabolites. However, the claimed invention comprises an unlimited amount of metabolic properties that could be affected by the large genus of DNAs in the large genus of host cells.

The specification at paragraph [0026] discloses that, "the present invention also relates to a method for the preparation of a desired metabolite by a transformed host cell comprising the steps of a) transfecting a host cell with at least one polynucleotide involved in the production of said desired metabolite and which is covalently coupled to a label which provides to the host cell a non-inheritable trait, b) isolating the transfected host cell, c) culturing the transfected host cell under proliferating conditions, d) culturing the transfected host cell under conditions wherein the desired metabolite is produced, and e) isolating the desired metabolite from the culture broth. In a preferred

embodiment of this latter method the polynucleotide is selected from the group consisting of DNA, RNA, short hairpin RNA, non-coding RNA, LNA, HNA and PNA. In a further embodiment of this method the polynucleotide modifies the cellular metabolism via redirecting metabolic fluxes towards said metabolite. Preferably, the desired metabolite is a primary metabolite such as an amino acid, a steroid or a nucleotide. More preferably, the desired metabolite is a secondary metabolite, such as an antibiotic, a vitamin, an anti-infective, a macrolide, a polyketide, a pheromone, an alkaloid or a drug".

The claimed invention is also directed to a label that does not produce an inheritable trait. The instant specification discloses that, "the present invention relates to a method for preparation of a modified host cell which comprises the steps of (a) transfecting a host cell with at least one compound of interest to which a label is covalently coupled and (b) isolating the transfected host cell, wherein the label provides to the host cell a non-inheritable trait. Modified host cells according to the invention can be directly separated from the non-modified host cell. To this end use is made of labels, which can be monitored at the modified cells (such as fluorescent labels) and which enable separation of the modified and non-modified host cells by suitable means. In case of fluorescent labels use can be made of a Fluorescent Activated Cell Sorter. Suitable compounds of interest according to this invention are compounds, which enable to change permanently or transiently a metabolic property of the host cell. Examples of compounds are polynucleotides, proteins or metabolites. The host cells modified according to the present invention can be used for the production of proteins,

metabolites and cell biomass" (see paragraph [0026]). The specification exemplifies for example a fluorescent label, however there is no indicia of for example a enzymatic label or a radioactive label or magnetic label etc., that does provides a non-inheritable trait. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

According to MPEP 2163.A.I, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". The Court addressed a similar argument in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). The *Rochester* Court found this difference to be a "semantic distinction" and held that "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he

can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, '[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.'" Accordingly, in the instant case, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of metabolic properties which would undoubtedly involve a protein encoded by the polynucleotides claimed, however, said protein is not mentioned in the claims. Moreover, claim 1 for example does not provide a method step to culture the host cell or passage the cells to generate more progeny which would then possess the recited "permanent change", thus the invention is not adequately described.

Moreover, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. Claims 1-5, 7-9 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The claimed methods are missing critical or essential method steps needed to practice the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The claimed method does not recited a step to "culture" the transfected host cells or a step to multiply or passage the cells to be able to practice item (1b) of the claimed invention to achieve a cell that integrated the DNA which then produced a permanent change.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-5, 7-9, 15-20 and 27-38 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

(A) Claim 1(item b) is confusing for the recitation of "wherein said at least one polynucleotide permanently changes a metabolic property of the transfected host cell as compared to the non-transfected host cell", because the claim does not recite an encoded enzyme for example and said metabolic property would involve a pathway and a protein would effect said change, not the polynucleotide *per se* (see also claim 29 (c) with similar language). (B)The claim is also indefinite for the recitation of "wherein the label provides to the host cell a non-inheritable trait" because the specification indicates that the fluorescent label is diluted as the cell is passage to form a new progeny, however, the first generation progeny would conceivable have more of the label than subsequent generations, thus the fluorescence of the first generation of cells could be construed as an "in-heritable trait". (C) Claim 1 is confusing for the recitation of "wherein the label provides to the host cell a non-inheritable trait" as it is unclear whether this 'wherein clause' goes with item (a) or item (b). If it belongs with item (b), the word "and" should be inserted following "host cell;". (D) Claim 1 (b) lacks clear antecedent basis for the recitation of "the non-transfected host cell". (E) Claim 1(b) indicates that the isolated transfected host cell has a permanent metabolic property change compared to non-transfected host cell and it is unclear how a permanent change is determined since the claim does not recite a step to culture the transfected

host cell and isolate said cultured cell to determine the existence or permanence of a metabolic change. The dependent claims hereto are also included.

Claim 3 is indefinite for the recitation of "using means" as the metes and bounds of the claim language is undefined. The means of detection will vary depending on for example the type of label, therefore, the claim language is ambiguous.

Claims 6, 30 and 35 are indefinite for the recitation of "under proliferating conditions" because neither the claims nor the specification sets forth what those conditions are. See also claim 16 that has similar language.

Claim 8 is indefinite for the recitation of "altered" as it is unclear how the level is altered, for example, is the host cell over expressing the protein (see also claim 28).

Claim 15 is ambiguous, thus definite because it is unclear if the DNA or the fluorescent label in item (a) is the non-inheritable trait. Claim 15(e) is confusing as to what is the "experimental versus the control group", based on the present claim language. In addition, there is no nexus between this method step and the preamble as claim 15 does not clearly establish how the host cell is modified (i.e. is the modification simply the transfection of a heterologous DNA or the expression of a protein by said DNA that produces a change in a metabolic property), see also claims 16-20, 29-30, and 32-38.

Claim 16 is indefinite for the recitation of "said DNA is involved in production of the desired metabolite" as the claims are drawn to a method thus should provide how the DNA is "involved", therefore, the metes and bounds of the claim is undefined. The dependent claims hereto are also included.

Claim 20 is indefinite for the recitation of an "anti-infective" as the metes and bounds of the claim is unclear/undefined.

Claim 28 is indefinite for the recitation of "wherein RNA and protein expression levels are altered in the modified host cell" as it is unclear how these are altered based on the method steps of claim 15. In addition, claim 15 from which claim 28 depends is directed to a "DNA", thus the recitation of "RNA" is confusing (see also claims 33 and 37 with similar language).

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-4, 6, 8-9, 15-18, 28-30, 33-35 and 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff et al. (U.S. Patent No. 6,262,252, July 17, 2001).

Wolff et al. teach a general method of covalently attaching a label to a target molecule using detectable fluorescent tags (see paragraph 4 and 15). Wolff et al. specifically teach a method for covalently attaching a fluorescent label to a nucleic acid (see claims 1-8 of the patent). Wolff et al. teach cells transfected with a DNA (see paragraph 227). In addition, Wolff et al. teach gene transfer (see paragraph 57). Wolff

et al. teach means of isolation (see paragraphs 95, 105 and 107). At paragraphs 227 and 229, Wolff et al. teach that the cells are transfected with the DNA and then cultured, fixed and analyzed via a fluorescent microscopy. The cells are compared with cell with unlabeled DNA. Thus, claims reciting isolation of cells with the labeled DNA and multiplying the cells is anticipated. Further, as protein expression occurs from the integrated DNA, it would inherently produce a metabolic change (i.e. a metabolite (amino acid)). The labels utilized by Wolff et al. are for example fluorescein, rhodamine, digoxin (see column 6 of the patent), thus would not produce an inheritable trait, especially since the instant application also utilizes fluorescein. Therefore, the limitations of the claims are met by the reference.

8. Claims 1-4, 6, 8-9, 15-18, 28-30, 33-35 and 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (AAPS Pharmsci, 1999, cited on the IDS filed January 18, 2007).

Johnson et al. teach a method for monitoring transfer of DNA during transfection, said method involving labeling a plasmid DNA with fluorescein-12-dUTP, flow cytometric detection and sorting of the fluorescent transfected cells (see pages 1-6). Therefore, the limitations of the claims are met by the reference. The reference teaches culturing the cells, sorting the cells and analyzing individual cells (see pages 2-4 of the reference). Johnson et al. utilized a fluorescein label as in the instant case thus the label would inherently not provide an inheritable trait. Further, claims reciting isolation of cells with the labeled DNA and multiplying the cells is anticipated. Further,

as protein expression occurs from the integrated DNA, it would inherently produce a metabolic change (i.e. a metabolite (amino acid)). Therefore, the limitations of the claims are met by the reference.

Response to Arguments

9. Applicant's comments have been considered in full, however, are not persuasive. Note that the art rejections of record remain and have been amended. Note also that a new ground of rejection has been instituted under 35 USC 112 first paragraph, enablement for the reasons stated above.

Regarding the rejection under 35 USC 112 first paragraph written description applicant states that, "The specification teaches a representative number of species within the claimed genus. In particular, it was alleged that the genus of host cells, polynucleotides, labels, and metabolic properties are not adequately described in Applicant's specification. Multiple species within each genus are well known to the skilled artisan. Host cells may be prokaryotic cells (i.e. bacteria)…". The claims broadly recite modifying any host cell, transfecting said host cell with any one or more polynucleotide that is covalently coupled to any label, wherein said polynucleotide permanently changes any metabolic property of the host cell (see for example claim 1). No specific embodiment is recited in the claim. Further, Applicant's statement that a

host cell may be prokaryotic such as bacterial is understood, however, the specification exemplifies *penicillium chrysogenum* and that example is not representative of the large variable genus of host cells encompassed in the claims. Further, applicant's contemplate the metabolic change to mean an antibiotic, a vitamin, a drug, a macrolide, a polyketide, a pheromone, an anti-infective etc. which is a very broad genus.

In addition, Applicant provides a discussion of the *Univ. of Rochester v. G.D. Searle & Co.* indicating that the fact pattern differs from the instant application. Applicant's comments are noted but not persuasive. The rejection has been amended to clarify the issues. The issue that remains is that the claimed invention is directed to any metabolic change such as a vitamin, or antibiotic or steroid or nucleotide etc., which is a large variable genus not adequately described. To simply indicate that any host cell transfected with any DNA will result in a permanent metabolic change with a non-inheritable trait from the label wherein the label can be fluorescent or enzymatic etc. is insufficient to demonstrate possession of the claimed method.

Applicant is reminded that "The 'written description' requirement.., serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed ....The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005). The purpose of the written description requirement "is to ensure that the scope of the right to exclude ... does not overreach the scope of the inventor's

contribution to the field of art as described in the patent specification." Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345-46 (Fed. Cir. 2000). The goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4 (CCPA 1977) "A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date." *In re Glass,* 492 F.2d 1228, 1232 (CCPA 1974). A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may also be subject to rejection under 35 U.S.C. 112, para. 1, as not enabling, or under 35 U.S.C. 112, para. *2. In re Collier,* 397 F.2d 1003 (CCPA 1968)".

"[E]ssential material" to an application is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. § 112).'" M.P.E.P. § 608.01(p)(B), at 600-35 (1983). *Quaker City Gear Works', Inc. et al. v. Skil Corporation,* 747 F.2d 1446,1455 n. 10 (Fed. Cir.1984)". Additionally, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991),* states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed

genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

The enablement rejection of record is withdrawn, however, a new rejection has been instituted for the reasons set forth above. Thus applicant's comments are moot and will not be addressed herein.

Note that the art rejections of record remain under 35 USC 102. Applicant state that the Wolff et al. reference is not relevant as they did not follow the protocol of the instant application. Applicant further state that the claimed method requires "isolation of the transfected host cells". It is also stated that, "Applicant's sorting of fluorescent cells from non-fluorescent cells resulted in isolation of the transfected cells which is lacking in Wolff". This argument is not persuasive as in deed Wolff et al. performs isolation as the cells are sorted and analyzed with respect to the fluorescent labeled DNA cells compared to cells with non-labeled DNA (see paragraphs 227 and 229 in the Wolff et al. patent). It is also stated that Wolff et al. does not change a metabolic process, however, the patented method employs a DNA labeled with the same fluorescent label used in the patent and the claims are broadly drawn to any DNA and host cells with any label. It is also stated that the claimed invention requires stable transfection, not shown by Wolff. This argument is not persuasive as applicant's are arguing a limitation not present in the claims, the claims are drawn to transfected cells

not stably transfected cells. Moreover, selection pressure is utilized in the reference, thus the DNA would be integrated into the genome. The reference also teach that the cells with the transfected labeled DNA is cultured and incubated (proliferating conditions). With respect to the Wolff reference applicant state that Danko et al. teach the same DNA as the Wolff patent and found only temporary effects on gene expression. This argument is not persuasive as the Danko et al. reference does not refer to the disclosure in Wolff. Further, the instant specification discloses at paragraph [0047] and [0045] that [T]his example demonstrates that applying directly detectable signals (in this case fluorescein) covalently coupled to DNA as a means of selecting and sorting the desired, modified cells results in cells in which the polynucleotide of interest triggers permanent metabolic changes. The results shown in table 1 demonstrate that protoplasts can resist the pressure in the FACS. Due to some clumping of protoplasts high and low scatter populations were isolated (see table 1). Only, cells with high scatter gave amdS positive clones (see sample E, table 1), demonstrating integration of fluorescent labeled DNA. So, after growing on synthetic media these cells lost the non-inheritable fluorescein marker, but retained the gene of interest". Thus, it appears the modification in the cell is being attributed to the DNA with fluorescein. Note that the cited Wolff reference also teach the use of fluorescein coupled to a plasmid, therefore the cell is inherently modified. Thus, applicant's arguments are not persuasive.

The same reasoning is provided for the Johnson reference. With regard to the Johnson reference applicant opines that gene transfer did not occur. The Johnson reference on page 2, second paragraph disclose that "this article describes a method for

monitoring the kinetics of the transfer of exogenous DNA during transfection....this method could detect cells containing internalized DNA as early as 1 hour after transfection and provide the intracellular location of the transferred DNA" (page 2). It is also disclosed in the materials and methods, that "a plasmid was labeled with fluorescein-12-dUTP (using nick translation). Thus both references are pertinent to the claimed invention, therefore, the rejections remain.

Conclusion

9. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Hope A. Robinson/

Primary Examiner, Art Unit 1652

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